Response

1. Claims 1-2 and 7-9 are amended. Claim 16 is new. Basis for these amendments is found in the claims as originally submitted and in the specification as filed. Basis for amended claim 1 is found, e.g., on p. 8-9, p. 11, ll. 19-21, p. 14, ll. 1-2, as well as prior claim 7; for amended claim 2, e.g., at p. 12, ll. 26; for amended claim 7 e.g., at p. 17; for amended claim 8, e.g., at p. 27; for amended claim 9, e.g., at p. 24; and for new claim 16, e.g., at at pp. 24-25 and withdrawn claim 12. No new matter has been added. Claims 3-6 and 10-15 are withdrawn. Claim 1 was amended to provide greater clarity and focus prosecution on the subject matter of greatest immediate interest to Applicants. As the remaining pending claims were then somewhat duplicative of claim 1 as amended, these claims were amended to provide dependent claims to particular embodiments of the invention. All amendments are without prejudice to the Applicant's right to pursue the original or additional scopes in subsequent divisional or continuation filings.

2. The specification was objected to in that the title was deemed not descriptive. The title has been amended accordingly.

3. *Rejections under 35 U.S.C. §112, first paragraph, scope of enablement*

Claims 1, 2, 7 - 9 are all rejected for lack of enablement. This rejection is largely mooted by the amendments to the claims. The clams as amended specifically recite that the condition to be treated is asthma and the targets of the immunization are specific cytokines, e.g., eotaxin and IL-5.

Applicants respectfully submit that the use of vaccines to generate antibodies is a mature art, so that the guidance required for enablement is not that great, and that the specification moreover provides a highly detailed teaching in the selection of immunogenic fragments of the target cytokines, effective conjugates and methods for making conjugates, effective adjuvants, and optimal formulations.

It is well established that the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only after the examiner provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *Id.*; see also *In re Bundy*, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981).

In this case, Applicants respectfully submit that the Examiner has not cited any reference or provided any evidence suggesting that the specific methods, which are specifically targeted to this particular address the concerns known in the art, would not work in this case.

A consideration of the factors set forth in *In re Wands*, 858 F.2d 731 (Fed.Cir. 1988) strongly supports finding of enablement in this case. In *Wands*, the Court of Appeals for the Federal Circuit reversed the Patent Office's finding of nonenablement and identified a variety of factors which may be relevant to whether practicing a claimed invention would require undue experimentation: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. As the *Wands* court held, whether undue experimentation is required is not a single, simple factual determination, and no one factor is necessarily determinative. Rather, enablement or lack of enablement is determined by weighing all of the applicable factual considerations. Applying the *Wands* factors to the instant case, it is clear that practicing the instant invention would not require undue experimentation, as the specification provides considerable guidance and exemplification for making the subject vaccines (albeit no clinical trials), the prior art relating to vaccine production is extensive, the skill of those working in the field is very high, the level of predictability is in some respects greater than for a typical small molecule pharmaceutical in that the claimed method is highly specific for selected targets, e.g., eotaxin and IL-5, which are known to be biologically relevant.

The Examiner argues, however, that "Many promising treatments and therapies have been identified via *in vitro* experiments, and have not lived up to expectations when tested *in vivo*. In fact the number of such treatments, which have failed to live up to their promise exceeds those, which have performed as hoped by orders of magnitude." Yet the Examiner is well aware that applications for pharmaceutical inventions are typically filed years before clinical data becomes available. Were this not permitted, patent protection for pharmaceuticals would be unavailable in most cases, as an enabling disclosure could not be filed until after successful completion of clinical trials, by which time the compounds and their utilities would likely be no longer novel. Applicants respectfully submit that the Examiner's suggestion that clinical data is required to demonstrate enablement of pharmaceutical therapies is simply not supported by the Federal Circuit's case law.

In a recent case, *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir 2006)(copy attached), the Federal Circuit addressed the enablement and written description requirements in the context of pharmaceuticals, and vaccines in particular. This case involved an interference directed to a vaccine using a live poxvirus wherein the poxvirus is lacking an essential gene and so cannot replicate except in a helper cell line transformed with the deleted essential poxvirus gene. The junior party in the interference argued that the senior party's disclosure did not satisfy the written description and enablement standards, and thus was not entitled to the earlier filing date. The senior party to the interference did not actually identify any essential poxvirus genes, he had no examples of any poxvirus vaccines, and the specification dealt mostly with herpes viruses, poxvirus vaccines being mentioned only in the general description. The PTO and the Federal Circuit nevertheless found the senior party's application to be enabled. In applying the *Wands* factors, the Federal Circuit emphasized that the existence of publications which disclosed poxvirus essential genes was sufficient to provide enablement for the claims of the application, even though such genes were not disclosed specifically in the application. *Id.* at 1365.

As the disclosure in this case is clearly far more specific and detailed than the disclosure for the vaccines claimed in *Falko-Gunter Falkner*, in that the structure of the essential components of the vaccine is defined and set forth clearly, Applicants respectfully submit that

the standards for enablement are met in this case, and the rejection for lack of enablement should be withdrawn.

3b. *Rejections under 35 U.S.C. §112, first paragraph, written description*

Clams 7-9 are rejected for inadequate written description. As claims 7-9 have been substantially amended, this rejection is moot. Further to the discussion above, however, Applicants note that in the context of written description for a claim to vaccines, the Federal Circuit has held that (1) examples are not necessary for written description, (2) actual reduction to practice is not required, and (3) there is no *per se* rule that an invention that involves a biological macromolecule must contain a recitation of known structures. *Falko-Gunter Falkner, discussed supra,* 448 F.3d at 1366. Clearly the written description for the claims in this case exceeds the minimum standards for an invention of this type as established in *Falko-Gunter Falkner*. Applicants respectfully request that this rejection be withdrawn.

4. *Rejection under 35 U.S.C. §112, second paragraph - indefiniteness*

Claims 1, 2 and 7-9 are rejected as indefinite. As the terms objected to no longer appear in the claims, this rejection is moot. Applicants respectfully request that this rejection be withdrawn.

5. *Rejections under 35 U.S.C. §103 - obviousness*

5a. Claims 1-2 and 7-9 are rejected as obvious over WO 03/0401164. The Examiner argues that, although this reference does not specifically teach administration vaccines for both eotaxin and IL-5, this combination would nevertheless be obvious because, "the artisan would have expected equal success using both components together to obtain a synergistic effect. . . . The combination would have been obvious to the skilled artisan and the results achieved would have been expected." There is an evident contradiction between this statement and the Examiner's rejections under 35 U.S.C. §112, first paragraph based on unpredictability of the art, etc.

With regard to claim 1, there is no teaching in the '164 application to combine vaccination for multiple cytokines, e.g., eotaxin and IL-5. There is likewise no teaching to use immunogenic carriers other than virus-like particles.

5b. Claims 1-2 and 7-9 are also rejected as obvious over WO 00/65058 (disclosing in view of Ponath, et al. US 7,265,201.

The '058 application discloses fusion peptides to raise an antibody response to IL-5. It does not disclose combination vaccines, nor does it disclose the immunogenic conjugates as claimed.

Ponath discloses eotaxin and methods of making antibodies to eotaxin. These antibodies are said to have utility in as drugs or in diagnostic or in vitro applications, but Ponath does not disclose therapeutic vaccines, let alone methods utilizing combinations of therapeutic vaccines.

Applicants respectfully traverse these obviousness rejections, as a *prima facie* case of obviousness has not been established. An obviousness determination requires four kinds of factual inquiries:

(1) the scope and contents of the prior art;

(2) the differences between the prior art and the claims at issue;

(3) the level of ordinary skill in the pertinent art; and

(4) any objective indicia of success such as commercial success, long felt need, and copying.

KSR Int'l., Co. v. Teleflex, Inc., 127 S. Ct. 1727, 1735 (2007) (citing *Graham v. John Deere Co.*, 383 US 1, 17-18 (1966)). The Supreme Court in KSR recognized that a showing of "teaching, suggestion, or motivation" to combine prior art could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 USC 103(a). *Id.* at 1741. The Supreme Court specifically stated that "it will be necessary . . . to determine whether there was an apparent reason to combine [or modify] the known elements [in the prior art] in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made *explicit*." Id. at 1740 - 41 (emphasis added).

It is therefore the Examiner's burden in asserting *prima facie* obviousness to provide evidence of some motivation or rationale for making a change over the art. *Takeda Chemical Industries, Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350 (Fed.Cir. 2007).

No such evidence has been provided in this case. The Examiner asserts that the claimed methods to treat asthma using vaccine combinations to selected cytokines to treat asthma would be obvious and would be expected to succeed. Yet despite the long felt need to develop effective treatments for asthma, which address the harmful immune response directly rather than merely its symptoms, and despite the evident skill, creativity and thoroughness of the authors of the references cited, these references fail to disclose or suggest the Applicants' claimed invention, or anything similar. This strongly suggests that perhaps the combination of different therapeutic vaccines to treat asthma was not obvious to the authors of these references or others of skill in the art at the time, but only now appears obviousness with hindsight.

Not only are the combinations unobvious, but the claims, moreover, are now limited to use of particular conjugates, which are not disclosed or suggested for use in a method as claimed.

Applicants therefore respectfully request that the obviousness rejections be withdrawn.

As a petition for a three month extension of time is submitted herewith, it is believed that no additional fee is required; however, should any fee be required, please charge the same (or credit any overpayment) to Deposit Account No. 50-4255.

Reconsideration and withdrawal of the rejection and a speedy allowance of the claims submitted is respectfully requested. The Examiner is invited to contact the undersigned by telephone in the event of any questions or if the Examiner believes that an interview could be productive.

Respectfully submitted,

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